Remarks

Applicants thank the Examiner for the interview held on September 9, 2008, with Applicants' representatives. As outlined in the Interview Summary dated September 12, 2008, Applicants' representatives explained the nature of the invention and pointed out the differences between the present invention and the prior art. The art rejection and written description rejection of record in the Office Action of April 24, 2008 were discussed and it was agreed that Applicants would file a response taking into account the Examiner's comments.

Amendments to the Claims

Upon entry of this Amendment, claims 20-25, 28-30, 32-39, 42 and 45-61 will be pending. Applicants have amended independent claims 20 and 48, currently on file, to more clearly define the scope of protection being sought. Claims 25 and 56-58 have been amended for consistency. Claims 27, 43 and 44 have been cancelled without prejudice or disclaimer. New claims 59 to 61 have been added to claim alternative embodiments of the invention. Support for the amendments and new claims can be found throughout the specification as filed, for example, in Examples I - IV.

35 U.S.C. 112, first paragraph (Written Description)

The Examiner has maintained the rejection of claims 20-25, 27-30, 32-39 and 42-58, under 35 U.S.C. 112, first paragraph, alleging the claims fail to comply with the written description requirement. The Examiner stated that Applicant's arguments have been fully considered but fail to persuade. The Examiner agreed that cloning and generation of various modified PapMV capsid proteins had been described in the art and indicated that the level of expectation of success of making modified PapMV protein was not questioned so long as the skilled artisan receives guidance with respect to what specific modifications should be made and what specific functions should the modifications result in. However, the Examiner alleged that the specification does not disclose a single species of a deletion, insertion or substitution of the amino acids within the PapMV capsid protein. The Examiner stated that although the references by Lee-Shanok, Ikegami and Trembley specifically disclose substitutions and deletions of

particular amino acids within the PapMV coat protein, the art does not disclose amino acid insertions encompassed by the claims. The Examiner acknowledged that the claims recite the function such as "assembling to form said VLP," but alleged that because of an absence of a representative number of species (such as specific structures of PapMV proteins, for example particular amino acids being mutated or deleted) for the claimed genus in the specification, that Applicants were not in possession of the claimed invention.

Applicants respectfully traverse the Examiner's rejection for the following reasons. As noted in Applicant's previous response, the claims currently on file (*i.e.* the presently claimed invention) are directed to a method that comprises administering to an animal an antigen and an effective amount of a defined adjuvant, specifically papaya mosaic virus (PapMV) or a VLP derived from the PapMV coat protein. As previously discussed, while various plant viruses and plant virus VLPs, including PapMV and PapMV VLPs, were known in the art, the immunopotentiating, or adjuvant, properties of such particles had not been previously recognized. The invention as presently claimed relates directly to this newly identified and surprising function of PapMV and PapMV VLPs and to the recognition that assembly of the PapMV coat protein into a specific structure, a VLP, maximizes this adjuvant function (see, for example, page 12, paragraph 0055).

The instant specification provides extensive description relating to the claimed method for taking advantage of the first-described recognition of the immunopotentiating properties of a PapMV VLP. For example, as outlined in Applicants previous response, the specification describes and illustrates the structure of the VLP itself and the function of the VLP as an adjuvant, or immunopotentiator. The instant specification also clearly describes and demonstrates this functional characteristic of immunopotentiation for the PapMV VLPs, as well as for PapMV, and describes the correlation between this functional characteristic and the VLP structure. Methods of making the VLPs from PapMV coat protein are also described in the instant specification. As such, Applicants maintain that the description provided in the specification in its entirety is more than sufficient to convey to one skilled in the art that, at the time the application was filed, Applicants had possession of the claimed invention with regard to the application of both unmodified and modified PapMV VLPs having immunopotentiating properties.

With respect to the Examiner's assertion that the instant specification fails to provide a single species of a modified coat protein, Applicants respectfully disagree. Applicants respectfully direct the Examiner to the description in the present application relating to the construction and testing of several coat proteins having a fusion of an immunogenic peptide at the C-terminus, *i.e.* "species" of coat proteins that have been modified (see Examples I, III and IV). As illustrated, for example in Figures 2 and 3 of the application, Applicants also demonstrated that these C-terminally modified mutant coat proteins are able to assemble into VLPs, indicating that these modifications are well tolerated. Based on these results as well as information available in the art, Applicants had recognized that certain regions of the coat protein were more amenable to modification without affecting the ability of the coat protein to assemble than others and had provided teaching to this effect in the specification (see, for example, page 12, paragraph 0056, which indicates that for fusions of the coat protein with an immunogen, for example, the immunogen can be "disposed on the amino or carboxy terminus, or inserted in an internal loop disposed on the outer surface of the CP. This can result in improved assembly as compared with the assembly of particles having a second portion on another location of the CP…." [emphasis added]; page 14, paragraph 0062, which indicates that the immunogen portion is "preferably disposed at or adjacent the C-terminus of the coat protein," and page 14, paragraph 0063, which indicates that the polynucleotide encoding the immunogen can be "inserted at or adjacent a terminus of the polynucleotide encoding the coat protein" and that it "is not necessary for the viral portion to comprise a whole virus coat protein").

Moreover, as discussed in Applicants' previous response, and acknowledged by the Examiner, various modified PapMV capsid (coat) proteins had been described in the art, for example, in Lee-Shanok, Ikegami, and Sit & AbouHaidar, as referenced previously, and as such, an extensive description of modified PapMV coat proteins should not be required in the instant specification (see MPEP at §2163, which states "Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d

1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)"). Moreover, the art also examined in detail the ability of these modified coat proteins to form functional viral particles and identified certain types and positions of mutations that could be tolerated. For example, as summarized at pages 146 to 148 of Ikegami and at pages 26 to 30 of Lee-Shanok, deletions, substitutions and insertions close to the N-terminus of the PapMV coat protein were well tolerated and did not affect infectivity or assembly of the viral particle. In contrast, large deletions at the C-terminus of the coat protein or mutations made at a distance from the C-terminus (such as a 1 amino acid deletion 32 amino acids upstream of the C-terminus (position 178)) impacted the ability of the virus to infect its host systemically. Specifically, Ikegami demonstrated that a substitution of Arg for Lys at position 3, an 18 amino acid deletion downstream from Arg3, and an 11 amino acid and 28 amino acid inframe insertion either as an addition to the N-terminus or as a replacement of the N-terminus of the coat protein were all tolerated and did not affect infectivity or assembly. Thus, contrary to the Examiner's assertion, the art not only provides several examples of substitutions and deletions, but also insertions and, as noted above, the instant application provides further examples of modified coat proteins. As such, Applicants assert that the combination of knowledge available in the art at the time the instant application was filed together with the teaching in the specification provides ample guidance as to what regions of the coat protein are amenable to modification while still retaining the ability of coat protein to assemble into a viral particle.

As previously discussed, and acknowledged by the Examiner, when the instant application was filed, protein engineering was a well-established art and the levels of skill and knowledge in this art were very high. Accordingly, Applicants maintain that the average worker in this highly developed art, in light of the guidance provided by the art and the instant application, would have readily understood what modifications could be made to the coat protein while still retaining the function of assembling into a VLP, as specified in the pending claims, and would have concluded that Applicants were in possession of the claimed invention at the time the application was filed.

Solely for the purpose of expediting the prosecution of the instant application, however, Applicants have amended independent claims 20 and 48 to more clearly define the subject matter for which protection is being sought. In particular, Applicants have amended these claims to delete reference to genetically modified coat protein.

Applicants submit that the amended claim set submitted herewith complies with 35 U.S.C. 112, first paragraph, and, therefore, respectfully request that this rejection be withdrawn.

35 U.S.C. 103

The Examiner rejected claims 20-25, 27-30, 32-39 and 42-58 under 35 U.S.C. 103(a) as being unpatentable over Lee-Shanok (Thesis for Degree of Master of Science, University of Toronto, 1999) in view of Ikegami (Thesis for Degree of Master of Science, University of Toronto, 1995). The Examiner alleged that Lee-Shanok discloses a method of potentiating an immune response against antigenic epitopes, specifically HCV epitopes recombinantly engineered to be expressed by papaya mosaic virus particles and that the papaya mosaic virus taught by Lee-Shanok has been genetically modified. The Examiner alleged that Lee-Shanok also teaches purified wild-type virus and oral administration of the papaya mosaic virus particles fused with the HCV epitope. While the Examiner has acknowledged that Lee-Shanok does not specify what kind of immune responses could be generated due to the administration of papaya mosaic virus particles fused with the HCV nucleocapsid, the Examiner has alleged that because Lee-Shanok discloses that papaya mosaic virus particles fused with the HCV nucleocapsid gene can be used as a vaccine and broadly refers to immune responses, it is expected that humoral and cellular responses are generated by the method disclosed by Lee-Shanok.

The Examiner, while acknowledging that Lee-Shanok does not teach the particular immunization schedule currently claimed, alleged that it would have been well within the knowledge and ability of the ordinary artisan to implement various immunization schedules including changing the order of antigen versus adjuvant being administered and that the current invention is unpatentable as being obvious over the prior art and the general knowledge in the art of vaccine development.

The Examiner further alleged that although Lee-Shanok does not expressly teach fusion of the antigens at a location other than N-terminus such that the antigen is disposed on the outer surface of the PapMV of VLP, in view of the teaching of Ikegami it would have been obvious to fuse or covalently attach foreign antigens at a location other than the N-terminus, such as for example at the C-terminus of the PapMV coat protein because Ikegami teaches that the N- and C-terminal regions of the potexvirus coat protein are exposed to the outer surface of the assembled viral particles. The Examiner further alleged that one would have been motivated to fuse foreign antigens at the C-terminus of the PapMV coat protein because this would facilitate the antigens to be disposed on the outer surface of the PapMV and that one would have had a reasonable expectation of success to fuse an antigen to the C-terminus of the PapMV because the recombinant technology techniques required for making protein fusion have been known and established in the art at the time of the present invention. The Examiner alleged that the present claims thus would have been *prima facie* obvious to the skilled artisan at the time when the invention was made.

Applicants respectfully traverse the Examiner's rejection for the following reasons. Firstly, as noted above, independent claims 20 and 48, currently on file, are directed to a method of potentiating an immune response against an antigen. As noted above, while various plant viruses and plant virus VLPs, including PapMV and PapMV VLPs, were known in the art, the immunopotentiating, or adjuvant, properties of such particles had not been previously recognized. The invention as presently claimed relates directly to this newly identified and surprising function of PapMV and PapMV VLPs. As such, claim 20 is not limited to PapMV VLPs fused or covalently attached to an antigen, but also includes administering PapMV itself, as well as PapMV VLPs, in combination with (*i.e.* not linked to) an antigen. Neither Lee-Shanok nor Ikegami provide any teaching or suggestion that PapMV or a PapMV VLP in and of itself could have immunopotentiating properties and thus nothing in either Lee-Shanok or Ikegami suggests that PapMV or PapMV VLPs could function as an adjuvant and simply be combined with an antigen in order to potentiate an immune response to that antigen. The object of both Lee-Shanok and Ikegami is to develop an antigen presentation system by using the PapMV coat

protein as a carrier for the antigen. In contrast, in the present application, Applicants are the first to demonstrate that surprisingly PapMV and PapMV VLPs can act as an adjuvant and, therefore, potentiate an immune response even to proteins that are themselves non-immunogenic (see, for example, page 9 (lines 18-20), Example II and Figures 5, 6 and 7).

Applicants assert that nothing in the cited art, therefore, teaches a method of potentiating an immune response using PapMV or a PapMV VLP as an adjuvant, nor does the art even suggest the use of PapMV or PapMV VLPs to potentiate an immune response when not linked to an antigen. Accordingly, Applicants maintain that claims 20 and 48, and claims dependent thereon, are not obvious in light of Lee-Shanok in combination with either the general knowledge in the art or with Ikegami.

For completeness, however, with respect to the Examiner's specific allegation that fusion of an antigen to a PapMV coat protein at a region other than the N-terminus would have been obvious over the combination of Lee-Shanok and Ikegami, Applicants provide the following comments. As indicated in Applicants previous response filed June 20, 2007, the objective of the research described in Lee-Shanok was to create an expression system for a PapMV coat protein fused to an antigen so that the engineered PapMV clone would be able to replicate in plants (see page 30, lines 20-21, of Lee-Shanok). As described in Lee-Shanok, the C-terminus of PapMV was known in the art to be required for infectivity (see Lee-Shanok at page 27, lines 4-5) and mutations in this region or in regions of the coat protein other than the N-terminus, or addition of non-viral nucleotides at the 3'-end of PapMV transcripts, had been shown to significantly decrease or abolish infectivity (see Lee-Shanok at page 26, line 10 to page 27, line 1). As such, Lee-Shanok teaches engineered PapMV with fusions at the N-terminus of the coat protein *only*.

Ikegami likewise is concerned with retaining the infectivity of the engineered PapMV. As outlined in the "Research Proposal" section of this thesis at page 18, lines 7-16, the general objective of the thesis relates to development of a foreign gene expression vector and an infectious plasmid to produce infectious transcripts *in planta*, to determine the feasibility of producing infectious genomic RNA transcripts in *E. coli* and to establish a PMV-protoplast

infection system. In order to retain infectivity, Ikegami, like Lee-Shanok, focused on attaching antigens to the N-terminus of the coat protein, as the prior art taught that mutations elsewhere in the coat protein abolished infectivity (see section entitled "Outline of the Strategy of a PMV Expression Vector" at pages 18, 18A and 18B of Ikegami). In this regard, Applicants note that they were in fact the first to identify the surprising ability of the PapMV coat protein to self-assemble into a VLP as described in the instant application (see, for example, page 19, paragraph 0071) and that this structure is necessary for adjuvant activity, irrespective of whether infectivity is retained. As such, Applicants assert that until the present application, the option of fusing an antigen to, or otherwise modifying regions of the PapMV coat protein other than the N-terminus, and in particular the C-terminal region, was considered unfeasible as the prior art taught that this would abolish infectivity, which in turn was required for replication of the virus. Accordingly, contrary to the Examiner's allegation, a worker skilled in the art having reference to the cited art, would not have been motivated to attach an antigen at a region of the coat protein other than the N-terminus.

Moreover, with respect to the Examiner's comment that Ikegami teaches that the C-terminus of the coat protein is exposed to the outer surface of the assembled viral particles, Applicants note that while at pages 128 and 131 of Ikegami, as referenced by the Examiner, it is stated that generally N- and C-termini of different potexvirus coat proteins are likely to be exposed at the outer surface of the assembled viral particles, at page 131, second paragraph, Ikegami states that surface mapping of the PMV (PapMV) coat protein suggests that the C-terminal residues are not exposed at the surface of the coat protein. At page 134, lines 6 to 7, Ikegami also indicates that the folding structure of PapMV coat protein is assumed to be analogous to the folding of PVX coat protein, which is described at page 131, last paragraph and page 134, lines 1 to 6, as having a C-terminus that is close to the surface of the coat protein, but exposed to the outside of the particle only when the N-terminus is trimmed (see also Figure 29, at page 136). Accordingly, Applicants assert that there is nothing in Ikegami or Lee-Shanok that would motivate the skilled worker to try to fuse or covalently attach an antigen to the C-terminus of the PapMV coat protein in order to dispose the antigen on the outer surface of the coat protein, nor would the skilled worker have any expectation that such an approach would be successful.

Solely in order to expedite prosecution of the instant application, Applicants have amended independent claim 20 to recite that the "antigen is not linked to said PapMV or VLP, or is fused ~~or covalently attached~~ to the C-terminus of a coat protein of said VLP ~~PapMV,~~". Applicants note that, as described above, the present application describes the construction and testing of several coat proteins having a fusion of an immunogenic peptide at the C-terminus (see Examples I, III and IV).

For the reasons set forth above, Applicants assert that the claim set submitted herewith complies with U.S.C. 35 103(a) and, therefore, respectfully request that the Examiner withdraw this rejection.

Conclusion

Applicants submit that all of the stated grounds for rejection have been properly traversed, accommodated or rendered moot. Applicants, therefore, respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favourable consideration of this Amendment and Reply is respectfully requested.

Respectfully,

JUNEAU PARTNERS, PLLC
Customer No. 50438
P.O. Box 2516
Alexandria, VA 22301

Todd L. Juneau
Reg. No. 40669